Title: Helicobacter Pylori in Otorhinolaryngology: Cause or Bystander

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ABSTRACT

The bacteria Helicobacter pylori (H. pylori) have been identified in extragastric tissues in the head and neck. The origin and pathogenicity of these bacteria in the head and neck are not known. The possible modes of spread are gastric reflux, a nasal or oral route. Laryngopharyngeal reflux has been identified as a contributing or causative factor in many sinonasal, pharyngeal, laryngeal and middle ear disorders. One of the possible modes by which laryngopharyngeal reflux may contribute is by seeding of the extragastric mucosa with H. pylori. The clinical significance of the discovery of H. pylori in extragastric tissues in the head and neck is unclear. There is no evidence of a pathologic or active role of H. pylori in otorhinolaryngological disorders. The suggestion that sinonasal cavities and pharynx may serve as a reservoir for H. pylori and that re-infection of the stomach occurs after eradication therapy awaits further studies for confirmation. No connection between H. pylori in the stomach and H. pylori, found in the head and neck, was proved. Also, these bacteria, found in the head and neck tissues, may be accidental or innocent bystanders which do not affect the pathways of otorhinolaryngological and gastroduodenal diseases. This review examines the evidence for a possible relationship of H. pylori with otorhinolaryngological diseases.

Keywords: Helicobacter pylori, otorhinolaryngology, laryngopharyngeal reflux, nasopharyngeal reflux

Introduction

The role of the bacteria Helicobacter pylori (H. pylori) in gastroduodenal disease has become well-established. The clinical significance of the discovery of H. pylori in extragastric tissues in the head and neck is unclear. This review examines the evidence for a possible relationship of H. pylori with otorhinolaryngological diseases.

The bacteria Helicobacter pylori in nose and paranasal sinuses

Chronic rhinosinusitis (CRS) is a clinical syndrome with many extrinsic and intrinsic etiological factors. It is felt that, among other potential factors, bacterial infection, bacterial colonization, bacterial allergy and bacterial superantigen may play a causative or contributory role. Gastroesophageal reflux, or more precisely nasopharyngeal reflux, is thought to be a contributing factor in refractory CRS [1]. The exact mechanism by which nasopharyngeal reflux may contribute is not known.
possibility is a sowing of the nasal mucosa with *H. pylori*, bacterium prevalent in gastric contents. *H. pylori* was found in nasal cavity and paranasal sinuses (Figure 1).

Özdek et al. [2] were the first who reported the presence of *H. pylori* in the sinus mucosa. Using nested polymerase chain reaction (PCR), *H. pylori* was detected in ethmoidal mucosa in four of 12 CRS patients, but it was not detected in 13 CRS-free patients with concha bullosa. Interestingly, using real-time PCR, Ozyrt et al. [3] detected *H. pylori ureA* gene more often in normal nasal mucosa than in nasal polyps samples (70% vs 59%, respectively). *H. pylori cagA* was identified in both *H. pylori*-positive normal nasal mucosa and nasal polyp samples (90% and 79%, respectively). Conversely, in the study of Burduk et al. [4], all of 30 nasal polyps and concha bullosa specimens were *H. pylori cagA* negative, but *H. pylori ureA* was found by PCR in all of 30 nasal specimens. In contrast to aforementioned studies, Ozcan et al. [5] reported that all nasal polyps from 25 patients were *H. pylori* negative by immunohistochemistry (IHC). Using PCR and Giemsa stain Cedeno et al. evaluated *H. pylori* in 28 children with CRS without polyps. Highly sensitive and specific primers ureC, vacA, cagA and babA were used but *H. pylori* was not detected in samples from the antral lavages or adenoids [6].

The following studies have raised a question about an active role of *H. pylori* in CRS. Compared with rhinologic patients without CRS, a statistically significant higher prevalence of sinonasal *H. pylori* in patients with CRS was found [7,8]. Koc et al. [7] reported that nasal polyps were positive in six of 30 CRS patients, whereas none of the control group samples were positive for *H. pylori* using IHC. In the study of Kim et al. [8], nasal specimens in 12 (out of 48) CRS patients and in one (out of 29) patient without CRS were *H. pylori* positive by both rapid urease test (RUT) and IHC analysis. There was no significant difference between *H. pylori positive* and *H. pylori negative* CRS patients comparing their preoperative rhinosinusitis symptom scores and the preoperative disease extent assessed by sinus computed tomography scoring system. A great proportion of degenerative coccoid shapes were found by IHC [8]. Kariya et al. demonstrated that whole-cell proteins of *H. pylori* in a viable but not culturable state, not exclusively live bacteria, can induce immunological inflammation in extragastric epithelium [9]. It has been suggested that these coccoid forms constitute a dormant resistant form of the bacterium which may revert into an infectious spiral form under the appropriate conditions and result in recrudescence of infection [10]. These findings imply that sinonasal cavities may be a reservoir for *H. pylori* and possible gastric re-colonization rather than that *H. pylori* has an active role in CRS. It is not clear why *H. pylori* has been presented in the coccoid form. One of possible
explanations may be a use of antibiotics [10]. Long-term antibiotic therapy (e. g., clarithromycin ~ 12 weeks) is included in the CRS treatment scheme and performed by a number of rhinologists. If there is a failure of maximal medical therapy after three months, sinus surgery is considered in medically refractory CRS, as it was done in aforementioned studies. Further, nasal cavities with good ventilation can provide an unfavorable oxygen excess. On the other hand, diseased ethmoids and massive polyposis can result in many narrow spaces which are poorly ventilated and drained. Such spaces can be favorable environment for microaerophilic H. pylori.

The results of Dinis et al. [11], regarding H. pylori and pepsin/pepsinogen I status in ethmoidal and sphenoidal mucosa, did not support the notion that H. pylori and laryngopharyngeal reflux had an important role in etiopathogenesis of CRS. No significant differences between CRS patients and CRS-free controls neither in blood and mucosa pepsin/pepsinogen I values nor in H. pylori sinonasal colonization were found. Sinonasal tissue pepsin/pepsinogen never rose above blood levels in both groups. This finding implies that H. pylori colonises the sinus mucosa via nasal route or via oral route rather than by gastric reflux. The authors state that, when in co-morbidity, the pathogenic mechanisms of H. pylori infection and reflux disease probably run in a parallel fashion, independent from each other [11]. Also, it is possible that H. pylori colonises vulnerable damaged sinonasal mucosa, as a favorable harbour, after CRS was already developed. In that case, H. pylori colonization is the consequence of CRS, not the cause.

A possible predictive value of H. pylori sinonasal colonization for efficacy of endoscopic sinus surgery in patients suffering from CRS with nasal polyps has been studied [12]. Nasal polyps in 28 (70%) of 40 patients were positive for H. pylori by IHC. There were no significant differences between the H. pylori positive and H. pylori negative group comparing the nasal polyp eosinophils, and the postoperative improvement of the CRS symptom scores. There was a prognostic value for endonasal findings: compared with CRS patients with H. pylori negative nasal polyps, patients with H. pylori had statistically significant greater improvement in postoperative endoscopic scores [12]. Physicians, who do not support „total war“ against H. pylori, might be delighted with this result. There is no consensus about Blaser’s suggestion that in addition to „bad“ and „very bad“ H. pylori, „neutral“ or „good“ ones exist as well [13]. A possible positive influence of H. pylori on asthma has been reported and explained by ability of some H. pylori compounds to drive T helper-1 polarization and to display a powerful inhibition of allergic T helper-2 response [14]. CRS is one of the most frequently encountered comorbid conditions associated with asthma. The current findings, regarding a
prognostic role of *H. pylori* in CRS, must be interpreted with caution. A status of the most important *H. pylori* virulence factors was not determined [12]. Theoretically, there may have been a state of preponderance of VacA negative and CagA negative strains which may have influenced histological and clinical findings. Further studies, including a larger sample size, stronger validated tools for assessment of CRS severity and determination of *H. pylori* virulence factors, are needed. The most relevant studies presenting the current state of knowledge on the relationship between *H. pylori* and CRS are shown in Table 1. A pathologic or active role of *H. pylori* in CRS were not established.

The bacteria *Helicobacter pylori* in pharynx

The study of Minocha et al. [15] has stimulated research on tonsils as a possible natural reservoir - extragastric site at which *H. pylori* evades treatment. They found a decreased prevalence of *H. pylori* gastric colonization in subjects with a history of tonsillectomy. The suggestion that tonsillectomy may protect the host against *H. pylori* infestation of the stomach has arisen, although reports to the contrary exist [16]. Fibrotic tonsils with debris trapped in crypts are a good environment and may be a permanent reservoir for microorganisms [17]. Tonsils, a component of mucosa-associated lymphoid tissue, are the first line of mucosal defence against invading pathogens. In the study of Skinner et al. [18], *H. pylori* seropositive patients exhibited a higher expression of inducible nitric oxide synthase in tonsillar macrophages than *H. pylori* seronegative patients. It can be hypothesized that *H. pylori* may be an initiating trigger or factor resulting in exaggerated inflammatory tonsillar response to otherwise commensal organisms [18].

Using PCR, Cirak et al. [19] found *H. pylori* DNA in tonsillar core or adenoid samples in seven (30%) of 23 patients. CagA gene was detected in adenotonsillar samples in five patients. Zhang et al. [20] detected *H. pylori* in pharyngeal mucosa in 19 (out of 50) patients with chronic pharyngitis and in none of 20 healthy controls. It can be speculated that *H. pylori* may be a cause of inflammation or a marker for reflux and chemical inflammation of pharyngeal mucosa caused by gastric acid [20]. Using immunofluorescence and immunoelectron microscopy, the study of Kusano et al. [21] on 55 patients with recurrent pharyngotonsillitis or IgA nephropathy (IgAN) demonstrated the coccoid form of *H. pylori* in the palatine tonsils of 43 patients. CagA was expressed in 38 of the 43 strains of tonsillar *H. pylori*. No tonsillar *H. pylori* could be cultured. All of 15 patients with gastric *H. pylori* had *H. pylori* in their tonsils. The prevalence of tonsillar *H. pylori* in patients with IgA nephropathy (100%) was
significantly higher than that in patients with recurrent pharyngotonsillitis (71%). It can be hypothesized that *H. pylori* may be a candidate for IgAN-pathogenic antigen [21]. It is not clear if the detection of adenotonsillar *H. pylori* represents transient or persistent colonization. Also, the origin of adenotonsillar *H. pylori* is not known. *H. pylori* may have reached pharynx via a nasal route or via an oral route or by refluxed gastric content. Lukeš et al. [22] detected different strains in the stomach and oropharynx in the same individuals. The oral presence of *H. pylori* without concurrent stomach infection was found. According to these findings, the *H. pylori* oropharyngeal colonization seems to be independent to the gastric infection.

This fastidious bacterium is difficult to culture from oropharyngeal specimens because of more robust flora competing for a growth. In the study on 62 palatine tonsils and 77 pharyngeal tonsils in 77 children [23], 17 palatine tonsils in 14 children were RUT positive and had negative *H. pylori* culture. Eight children had positive both RUT in tonsils and ^13^C-urea breath test. There was no significant difference between children with tonsillar hypertrophy and those with recurrent tonsillitis in *H. pylori* seropositivity [23]. Siupsinskiene et al. found significantly higher prevalence of tonsillar *H. pylori* in patients with chronic tonsillitis in comparison to patients with tonsillar hypertrophy. They also reported significant correlation of *H. pylori* colonization with laryngeal signs of laryngopharyngeal reflux [24].

Yilmaz et al. [25] were the first who isolated *H. pylori* from the pharyngeal tissue culture. Out of 22 children, there was a growth of *H. pylori* in cultures of adenoids and tonsils in 11 and 12 patients, respectively. These findings were supported by positive PCR. In contrast, all of the 25 adenoids tested were *H. pylori* negative by nested PCR in the study of Bitar et al. [26]. There are contradictory results regarding presence of pharyngeal *H. pylori* in the studies performed on the populations from the same country [25,26]. It is not known if a cognition of patchy distribution of *H. pylori* in the stomach may be applied to the pharynx. In that case, number of samples taken from one site can affect the results.

In the study of Vilarinho et al. [27] on 46 palatine tonsils and 55 adenoids in 62 children, three tonsils in two *H. pylori* seronegative children were IHC positive but all the specimens studied were negative by PCR, directed to the vacA gene, and by the fluorescence *in situ* hybridization with a specific *H. pylori* peptide nucleic acid probe. The authors do not consider adenotonsillar tissue in children as a permanent reservoir for *H. pylori* infection [27]. There is no evidence of a pathologic or active role of pharyngeal *H. pylori*. The suggestion that pharynx may serve as a reservoir for *H. pylori* and that re-
infection of the stomach occurs after eradication therapy awaits further studies for confirmation. This attitude is consistent with the results of other studies [6,18,28]. The most relevant studies presenting the current state of knowledge on the relationship between H. pylori and adenotonsillar pathology are shown in Table 2.

The bacteria Helicobacter pylori in larynx

Laryngopharyngeal reflux (LPR) is a form of extraesophageal reflux characterized by laryngopharyngeal symptoms such as hoarseness, globus pharyngeus, throat clearing and cough. The role of H. pylori toxins in gastric contents that reflux to the larynx and hypopharynx in laryngopharyngeal manifestations is uncertain. No relationship between gastric H. pylori infection and LPR was reported [29]. Conversely, Oridate et al. [30] demonstrated a lower laryngopharyngeal symptom-improvement rate influenced by acid-suppression therapy among H. pylori-seronegative patients than among H. pylori-seropositive patients with gastroesophageal reflux disease. In the study of Çekin et al. [31] using real-time PCR, laryngeal H. pylori and LPR were found in 56% and in 70% of 43 patients with laryngeal lesions, respectively. H. pylori was detected in 18 of the 30 LPR-positive patients and in six of the 13 LPR-negative patients. A statistically significant relationship of LPR positivity with malignant/premalignant laryngeal lesions and no association between laryngeal H. pylori and laryngeal lesions were found.

The bacterium H. pylori is the first formally recognized bacterial carcinogen [32]. A possibility that H. pylori may increase susceptibility to head and neck carcinoma, not just to gastric carcinoma only, is an important subject of research. The laryngeal epithelium has its origin in the respiratory diverticulum of the ventral wall of the foregut and develop embryologically from the same endodermal cells that line the gastric mucosa [33]. Compared with cancer-free controls, a significantly higher prevalence of H. pylori seropositivity in patients with laryngohypopharyngeal carcinoma was found [34]. Reports of the contrary also exist [35].

In the study of Titiz et al. [36], an association between laryngeal H. pylori and laryngeal carcinoma was found. All benign laryngeal lesions were H. pylori negative by PCR, but laryngeal H. pylori was found in 17 of 21 patients with laryngeal carcinoma. Of those 17 H. pylori-positive patients, H. pylori was detected in normal laryngeal tissue only, tumor tissue only and in both normal and tumor tissue in eight, one and eight patients, respectively. All tissue cultures were H. pylori negative [36]. In the
study conducted in Egypt [37], PCR was used to detect *H. pylori ureaA* and *cagA* genes in 49 patients with laryngeal carcinoma and 15 patients with laryngeal benign polyps. A significantly higher incidence of *H. pylori* was found in carcinoma specimens (65%) in comparison to benign polyps specimens (20%). These findings supported a positive association between *H. pylori* laryngeal colonization and susceptibility to development of laryngeal carcinoma [37]. Contradictory results suggesting the protective affect of laryngeal *H. pylori* against laryngeal carcinoma were reported by Amizadeh et al. [38]. Iranian patients with laryngeal carcinoma had lower incidence of laryngeal *H. pylori* and statistically significant lower incidence of *cagA* gene than those with benign laryngeal lesions [38]. Using PCR Yilmaz et al. detected laryngeal *H. pylori* in only one case out of 74 Turkish patients with laryngeal carcinoma [39]. The presence of laryngeal *H. pylori* DNA in all of 30 patients with benign laryngeal lesions [4] and in 59% of 29 patients with benign or malignant laryngeal diseases [3] was reported. *H. pylori cagA* was found in 23% and 82% of these *H. pylori*-positive patients, respectively [4,3]. Like in neighbouring organs, the character and origin of such *H. pylori* colonization are not determined. A descending or ascendant approach from nose, mouth, and pharynx or stomach are possible. A pathologic or active role of *H. pylori* in laryngeal disorders were not proved. It is plausible that improved knowledge on the mechanisms responsible for *H. pylori*-associated gastric carcinogenesis will enhance research on a relationship between *H. pylori* and laryngeal malignancies. The most relevant studies presenting the current state of knowledge on the relationship between *H. pylori* and laryngeal disorders are shown in Table 3.

**The bacteria *Helicobacter pylori* in middle ear**

Otitis media with effusion (OME) is a chronic inflammatory disease characterized by conductive hearing loss and the persistence of a middle ear effusion for at least three months without clinical signs and symptoms of active infection. It is not clear why OME develops. In the study of Tasker et al. [40], a possible role of gastroesophageal reflux in the disease pathogenesis has been studied. In 91% (out of 65) samples from children undergoing myringotomy for OME, pepsin/pepsinogen levels in the middle ear effusion samples were up to 1000 times higher than serum levels, indicating that the pepsin in the middle ear was almost certainly due to reflux of gastric contents. Immunohistochemical analysis of biopsy samples from the middle ear showed no evidence of pepsin production by the middle ear [40]. Reflux of gastric acid and pepsin into the nasopharynx and the Eustachian tubes may...
have led to chemical inflammation and edema of nasopharyngeal mucosa and Eustachian tube dysfunction. These findings suggest that anti-reflux therapy may come to play a part in the OME treatment.

Morinaka et al. [41] have reported that immunostained smears revealed *H. pylori* in 12 (80%) middle ear effusion specimens from 15 patients with OME, mostly adults. Since the adenoid tissue has been incriminated as a source of microorganisms causing middle ear disease, adenoidectomy is a common procedure as a part of the OME treatment. Although the study of Fancy et al. [42] demonstrated the *H. pylori* gene by PCR in 23 (32%) of 73 middle ear fluid samples from children with OME, the *H. pylori* prevalence rate in the adenoids of children with OME did not differ from those in the adenoids of OME free-children. Conversely, Bitar et al. [43] failed to detect *H. pylori* in all 28 middle ear effusion samples from 18 children with otitis media using culture and PCR. The study of Pitkäranta et al. [28] has shown *H. pylori* negative cultures of 12 middle ear fluid samples in all eight examined children with recurrent otitis media.

Yilmaz et al. [25] were the first who showed a growth of *H. pylori* in cultures of middle ear fluid and tympanic mucosa. Compared with the healthy ears of controls, a statistically significant higher prevalence of *H. pylori* in the middle ear of children with OME was found using culture and PCR. The presence of viable and culturable *H. pylori* indicate that the middle ear with insufficient ventilation can be a favorable environment for *H. pylori*. In the study on rabbits [44], after inoculation of *H. pylori* in tympanic cavity, *H. pylori* was cultured in six of eight ears with histamine-induced inflammation, but not in any of eight normal middle ears. According to the previously reported findings [25,40], transmission of *H. pylori* from stomach to the middle ear by reflux might occur in humans. Also, approach via a nasal route or via an oral route is possible. Association, not causation, of OME with reflux and *H. pylori* was established. It seems plausible that refluxed acid and pepsin or *H. pylori* or both together have a role in the pathogenesis of OME. It can be speculated that *H. pylori* may be a cause of inflammation, a marker for reflux and chemical inflammation caused by gastric acid, or an innocent bystander. The histopathological findings of rabbit middle ears with histamine-induced inflammation, inoculated by *H. pylori*, suggest that *H. pylori* can not initiate otitis media alone, but contributes to the inflammation process in the presence of an effusion [44]. The *in vivo* study on mice [9] indicated that *H. pylori* may cause immunological inflammation in middle ear epithelium. *H. pylori* whole-cell proteins, injected into the tympanic cavity directly, stimulated...
release of inflammatory mediators, and induced inflammatory cell infiltration into the middle ear epithelium in mice.

Saki et al. [45] investigated a possible relationship between *H. pylori* and tympanosclerosis. Using PCR they detected tympanal *H. pylori* in 34 (61%) of 56 Iranian patients with chronic otitis media. Their results suggested an association between *H pylori* and tympanosclerosis development. Nineteen patients with tympanosclerosis had statistically significant higher prevalence of tympanal *H. pylori* in comparison with 37 patients suffering from other forms of chronic otitis media (84% and 45%, respectively) [45]. Contradictory results suggesting a lack of association between *H. pylori* and tympanosclerosis were reported by Dinç et al. The tympanosclerotic plaques in all of their 35 patients with tympanosclerosis were PCR negative for *H. pylori* [46]. The most relevant studies presenting the current state of knowledge on the relationship between *H. pylori* and OME are shown in Table 4. A pathologic role of *H. pylori* in the middle ear disorders in humans was not established.

**Conclusions**

The bacteria *H. pylori* have been identified in extragastric tissues in the head and neck. The origin and pathogenicity of these bacteria are not known. The possible modes of spread are gastric reflux, a nasal or oral route. The clinical significance of such *H. pylori* colonization is debatable. No connection between *H. pylori* in the stomach and *H. pylori*, found in head and neck, was proved. The suggestion that sinonasal cavities and pharynx may serve as a reservoir for *H. pylori* and that re-infection of the stomach occurs after eradication therapy awaits further studies for confirmation. There is no evidence of an active role of *H. pylori* in otorhinolaryngological disorders and a cause-effect correlation was not established. These bacteria, found in head and neck tissues, may be accidental or innocent bystanders which do not affect the pathways of otolaryngological and gastroduodenal diseases. There is a lack of evidence to perform *H. pylori* testing for otorhinolaryngological diseases. Previous studies on this topic are conflicting. The role of *H. pylori* in some otorhinolaryngological disorders is likely to receive greater research attention.

**Recommendations for future research**

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Since the discovery of *H. pylori* has fundamentally changed paradigms regarding causation of gastric diseases, investigators should be open-minded about the possibility that *H. pylori* contributes to some head and neck diseases. More research on the bacterium’s infectious and immunological properties should test the hypothesis that *H. pylori* may cause head and neck diseases even far from the primary site of infection in the stomach by interfering with different biologic processes. Further studies on this issue will need to include a larger sample size, stronger validated tools for assessment of disease extent and severity; and, determination of a status of the most important *H. pylori* virulence factors. While respecting ethical standards, invasive determination of the stomach *H. pylori* status and typing of *H. pylori* isolates are needed in order to show if *H. pylori*, found in the head and neck, is the same as in the stomach. Continuous advancements in analytical technology and molecular techniques for bacterial identification should be used for accurate identification of *H. pylori*. Future studies should determine the modes of spread of the bacteria into the head and neck and whether colonization is occasional or persistent. More information about *H. pylori* activities in patients with oral, pharyngeal, and laryngeal carcinogenesis are warranted.

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Table 1. The studies presenting the current state of knowledge on the relationship between the bacteria *Helicobacter pylori* and chronic rhinosinusitis (CRS)

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Method</th>
<th>Specimen</th>
<th>Study group (total number)</th>
<th>Control group (total number)</th>
<th>Study group vs Control group</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Koc et al., 2004 [7]</td>
<td>IHC</td>
<td>Nasal polyp, middle concha</td>
<td>30 / 6</td>
<td>20 / 0</td>
<td>S</td>
<td>A possible involvement in the CRS pathogenesis</td>
</tr>
<tr>
<td>Dinis et al., 2006 [11]</td>
<td>PCR</td>
<td>CRS mucosa, normal sinus mucosa</td>
<td>15 / 6</td>
<td>5 / 1</td>
<td>NS</td>
<td>No significance of <em>H. pylori</em> for the CRS pathogenesis</td>
</tr>
<tr>
<td>Kim et al., 2007 [8]</td>
<td>IHC</td>
<td>Nasal polyps, nasal mucosa</td>
<td>48 / 12</td>
<td>29 / 1</td>
<td>S</td>
<td>A possible involvement in the CRS pathogenesis</td>
</tr>
<tr>
<td>Ozcan et al., 2009 [5]</td>
<td>IHC</td>
<td>Nasal polyp, nasal mucosa</td>
<td>25 / 0</td>
<td>14 / 0</td>
<td>NS</td>
<td>No presence of <em>H. pylori</em> in nasal polyps and normal nasal mucosa</td>
</tr>
<tr>
<td>Ozyrt et al., 2009 [3]</td>
<td>PCR</td>
<td>Nasal polyp, nasal mucosa</td>
<td>32 / 19</td>
<td>27 / 19</td>
<td>NS</td>
<td><em>H. pylori</em> encountered more often in normal nasal mucosa than in CRS mucosa</td>
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</table>

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IHC: immunohistochemistry; PCR: polymerase chain reaction; ESS: endoscopic sinus surgery; S: significant difference; NS: no significant difference

| Jelavic et al., 2012 [12] | IHC   | Nasal polyp | 28 / 28 | 12 / 0 | S | A possible prognostic value of *H. pylori* for the ESS outcome |

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Table 2. The studies presenting the current state of knowledge on the relationship between the bacteria *Helicobacter pylori* and adenotonsillar pathology

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Specimen</th>
<th>Method for H. pylori detecting</th>
<th>Study group (total number)</th>
<th>Control group (total number)</th>
<th>Study group vs Control group</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cirak et al., 2003¹⁹</td>
<td>Tonsil, adenoid</td>
<td>PCR</td>
<td>23 / 7</td>
<td>-</td>
<td>-</td>
<td><em>H. pylori</em> may colonise tonsil and adenoid</td>
</tr>
<tr>
<td>Bitar et al., 2005²⁶</td>
<td>Adenoid</td>
<td>PCR</td>
<td>25 / 0</td>
<td>-</td>
<td>-</td>
<td>No presence of <em>H. pylori</em> in adenoids</td>
</tr>
<tr>
<td>Zhang et al., 2006²⁰</td>
<td>Pharyngeal mucosa</td>
<td>TDI-FP</td>
<td>50 / 19</td>
<td>20 / 0</td>
<td>S</td>
<td>A possible involvement in the chronic pharyngitis pathogenesis</td>
</tr>
<tr>
<td>Yilmaz et al., 2006²⁵</td>
<td>Tonsil, adenoid</td>
<td>PCR, culture, culture</td>
<td>22 / 16</td>
<td>20 / 9</td>
<td>NS</td>
<td>Culturable <em>H. pylori</em> may exist in tonsil and adenoid</td>
</tr>
<tr>
<td>Kusano et al., 2010²¹</td>
<td>Tonsil</td>
<td>IF and IE microscopy</td>
<td>14 / 14</td>
<td>41 / 29</td>
<td>S</td>
<td>Tonsillar <em>H. pylori</em> may be a candidate for IgA nephropathy - pathogenic antigen</td>
</tr>
<tr>
<td>Vilarinho et al., 2010²⁸</td>
<td>Tonsil, adenoid</td>
<td>IHC, PCR-DEIA, PNA-FISH</td>
<td>62 / 2</td>
<td>62 / 0</td>
<td>-</td>
<td>Adenotonsillar tissue is not an extragastric reservoir for <em>H. pylori</em></td>
</tr>
<tr>
<td>Siupsinskiene et al., 2017²⁴</td>
<td>Tonsil</td>
<td>HC</td>
<td>62 / 35</td>
<td>35 / 11</td>
<td>S</td>
<td>A possible association with chronic tonsillitis and laryngopharyngeal reflux</td>
</tr>
</tbody>
</table>

¹⁹ Citation required
²⁶ Citation required
²⁰ Citation required
²⁵ Citation required
²¹ Citation required
²⁸ Citation required
²⁴ Citation required

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PCR: polymerase chain reaction; TDI-FP: template-directed dye-terminator incorporated with fluorescence polarization detection; IF: immunofluorescence; IE: immunoelectron; IHC: immunohistochemistry; HC: histochemistry; DEIA: DNA enzyme immunoassay; PNA-FISH: peptide nucleic acid-fluorescent in situ hybridization; S: significant difference; NS: no significant difference
<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Specimen</th>
<th>Method for H. pylori detecting</th>
<th>Study group (total number / H. pylori positive)</th>
<th>Control group (total number / H. pylori positive)</th>
<th>Study group vs Control group</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Titiz et al., 2008 [36]</td>
<td>MLL, BLL</td>
<td>PCR Culture</td>
<td>21 / 17</td>
<td>19 / 0</td>
<td>S</td>
<td>A possible involvement in the laryngeal carcinogenesis</td>
</tr>
<tr>
<td>Ozyurt et al., 2009 [3]</td>
<td>MLL, BLL</td>
<td>PCR</td>
<td>29 / 17</td>
<td>-</td>
<td>-</td>
<td>H. pylori may colonise MLL and BLL</td>
</tr>
<tr>
<td>Burduk et al., 2011 [42]</td>
<td>BLL</td>
<td>PCR</td>
<td>30 / 30</td>
<td>-</td>
<td>-</td>
<td>H. pylori may colonise BLL</td>
</tr>
<tr>
<td>Cekin et al., 2012 [31]</td>
<td>MLL, BLL</td>
<td>PCR</td>
<td>21 / 9</td>
<td>22 / 15</td>
<td>NS</td>
<td>No involvement in the laryngeal carcinogenesis</td>
</tr>
<tr>
<td>Amizadeh et al., 2015 [38]</td>
<td>MLL, BLL</td>
<td>PCR</td>
<td>72 / 24</td>
<td>72 / 33</td>
<td>S</td>
<td>A possible association with protection to development of laryngeal carcinoma</td>
</tr>
<tr>
<td>Barakat et al., 2016 [37]</td>
<td>MLL, BLL</td>
<td>PCR</td>
<td>49 / 31</td>
<td>15 / 3</td>
<td>S</td>
<td>A possible involvement in the laryngeal carcinogenesis</td>
</tr>
</tbody>
</table>

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MLL: malignant laryngeal lesion; BLL: benign laryngeal lesion; PCR: polymerase chain reaction; S: significant difference; NS: no significant difference
Table 4. The studies presenting the current state of knowledge on the relationship between the bacteria *Helicobacter pylori* and the middle ear disorders

<table>
<thead>
<tr>
<th>Author, Year</th>
<th>Method for <em>H. pylori</em> detecting</th>
<th>Specimen</th>
<th>Study group (total number / <em>H. pylori</em> positive)</th>
<th>Control group (total number / <em>H. pylori</em> positive)</th>
<th>Study group vs Control group</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pitkäranta et al., 2005 [28]</td>
<td>Culture</td>
<td>MEE</td>
<td>12 / 0</td>
<td>-</td>
<td>-</td>
<td>No presence of <em>H. pylori</em> in MEE</td>
</tr>
<tr>
<td>Morinaka et al., 2005 [41]</td>
<td>IHC</td>
<td>MEE</td>
<td>15 / 12</td>
<td>-</td>
<td>-</td>
<td><em>H. pylori</em> may exist in MEE</td>
</tr>
<tr>
<td>Bitar et al., 2006 [43]</td>
<td>Culture, PCR</td>
<td>MEE</td>
<td>28 / 0</td>
<td>-</td>
<td>-</td>
<td>No presence of <em>H. pylori</em> in MEE</td>
</tr>
<tr>
<td>Yilmaz et al., 2006 [25]</td>
<td>Culture, PCR</td>
<td>MEM, MEE</td>
<td>22 / 10</td>
<td>20 / 2</td>
<td>S</td>
<td>A possible involvement in the OME pathogenesis</td>
</tr>
<tr>
<td>Fancy et al., 2009 [42]</td>
<td>PCR</td>
<td>MEE</td>
<td>73 / 23</td>
<td>-</td>
<td>-</td>
<td><em>H. pylori</em> may exist in MEE</td>
</tr>
<tr>
<td>Saki et al., 2015 [45]</td>
<td>PCR</td>
<td>MEM</td>
<td>19 / 16</td>
<td>37 / 15</td>
<td>S</td>
<td>A possible involvement in the tympanosclerosis pathogenesis</td>
</tr>
<tr>
<td>Dinç et al., 2016 [46]</td>
<td>PCR</td>
<td>MEM</td>
<td>35 / 0</td>
<td>53 / 0</td>
<td>NS</td>
<td>No involvement in the</td>
</tr>
</tbody>
</table>
sclerotic plaques
tympanosclerosis
pathogenesis

MEE: middle ear effusion; MEM: middle ear mucosa; OME: otitis media with effusion; IHC: immunohistochemistry; PCR: polymerase chain reaction; S: significant difference
Figure 1. The nasal polyp: Brown stained immunoreactive structures above the epithelium represent the bacteria *Helicobacter pylori*. Immunohistochemistry with polyclonal rabbit anti-*Helicobacter pylori* antibody (peroxidase-antiperoxidase), light micrograph. ×1000